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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/539,407 | 01/17/2006 | Laurent Meijer | 040388-0131 | 4591 |

22428 7590 02/20/2009
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| EXAMINER | |
|---|---|
| SCHUBERG, LAURA J | |
| ART UNIT | PAPER NUMBER |
| 1657 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 02/20/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/539,407 | MEIJER ET AL. | |
| | Examiner | Art Unit | |
| | LAURA SCHUBERG | 1657 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 November 2008*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3-9 and 11-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9 and 11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

This action is in response to papers filed 11/24/2008. No claims were canceled or newly added. Claim 1 has been amended. Currently, claims 1, 3-9 and 11-14 are pending in the application.

### *Response to Arguments*

Applicant's arguments with respect to claims 1, 3-9 and 11-14 have been considered but are moot in view of the new ground(s) of rejection. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-9 and 11-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of inducing differentiation of supernumery hair cells and Deiters' cells in a mammalian developing organ of Corti, does not reasonably provide enablement for an *in vivo* method of inducing differentiation of supernumery hair cells and Deiters' cells in any organ of Corti of any specie. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Practicing such a method would require the skilled artisan to invest undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' "(Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the predictability or unpredictability of the art, (5) the relative skill of those in the art, (6) the amount or direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary.

N.B. MPEP 2164.04 states, "[w]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection" and that "[t]he language should focus on those factors, reasons,

and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims." Accordingly, the Factors most relevant to the instant rejection are addressed in detail below.

1-2 .Breadth of the claims and the nature of the invention..

Applicant's claims are directed to a method for inducing differentiation of supernumery hair cells and Deiters' cells in an organ of Corti in a subject comprising administering a composition comprising at least one CDK/cyclin kinase inhibitor that is a purine derivative and a pharmaceutically acceptable carrier, wherein the subject suffers from nerve deafness due to death of sensory hair cells and the composition is administered in an effective amount for inducing differentiation of supernumerary hair cells and Deiters' cells in an organ of Corti of the subject.

The claims are broad in that they encompass any specie of subject at any stage of development.

3-4. The state of prior art and the level of predictability in the art.

The prior art indicates that compounds with kinase inhibitory activity, such as CDK/cyclin kinase inhibitors are useful for the treatment of neurological disorders, including hearing loss (Santora et al., US 2002/0173507, page 15, para 361). These compounds are taught to be useful to prevent the phosphorylation of tau protein, which has no known connection to hearing loss as confirmed by Dr. Meijer. Administration of

purine derivatives of CDK inhibitors, such as roscovitine, indirubin and purvalanol are taught to be useful for treating neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease (Meijer WO 01/41768, page 1 and page 3). None of the prior art teaches using purine derivatives of CDK inhibitors for the treatment of sensory hearing loss or the treating of supernumerary hair cells and Deiters' cells in an organ of Corti. Lowenheim et al teach that it remains to be determined whether release from cell-cycle inhibition not only will cause cell proliferation in the organ of Corti, but also initiate further steps required for hair cell differentiation, maturation, and functional recovery to complete the hair cell regeneration process (Proc. Natl. Acad. Sci., page 4088, from IDS).

5. The relative skill in the art.

The relative skill in the art as it relates to the method of the invention is characterized by that of a M.D. or Ph. D. level individual.

6-7. The amount of guidance present and the existence of working examples.

Although the specification discloses methods of administration of CDK/cyklin kinase inhibitors *in vitro* to mammalian cells, there are no data on the effectiveness of CDK/cyklin kinase inhibitors used in an *in vivo* induction of differentiation of supernumerary hair cells and Deiters' cells in an adult organ of Corti in various species.

Applicant has not provided any evidence of success with the claimed method by administration to a subject. Applicant's disclosure appears to be speculative as to the success of the claimed method and does not provide substantial evidence that would establish the outcome with a reasonable expectation of success for the entire scope of the claimed invention. The state of the current art supports that to date no studies have reported regeneration of the auditory system. Significant gaps remain in our knowledge regarding the molecular interactions underpinning auditory functions, including the factors required for cellular regeneration and regulation of cochlear gene expression (see Hildebrand et al., page 233, conclusions). Breuskin et al teach that it remains to be established whether hair cells generated by transdifferentiation survive in the cochlear and whether they would become physiologically functional in the organ of Corti to restore impaired hearing even if they are not located at their initial position (page 8, conclusions). Even Malgrange teaches that there is currently no treatment able to stop the progression of a hearing loss or to restore a lost auditory function (abstract).

8. The quantity of experimentation necessary.

The amount of experimentation that is required is undue: while the administration of CDK inhibitors to *in vitro* cell cultures is routine, a method of further administering purine derivatives of CDK kinase inhibitors to subjects of various species for the induction of supernumery hair cells and Deiters' cells in an organ of Corti is not routine and requires more experimentation. Applicant's disclosure lacks specific

information on a range of subjects both mammalian and non-mammalian and stages of Corti development beyond that of developing (such as the adult Corti). Applicant's own current publications as well as the current art cast doubt as to the efficacy of the claimed method with regard to the treatment of nerve deafness.

Therefore, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

All other claims depend directly or indirectly from rejected claims and are, therefore, also rejected under USC 112, first paragraph for the reasons set forth above.

## ***Conclusion***

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA SCHUBERG whose telephone number is (571)272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/

Primary Examiner, Art Unit 1651

Laura Schuberg